



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
CHEMICAL SAFETY AND  
POLLUTION PREVENTION

**MEMORANDUM**

**Date:** August 29, 2014

**SUBJECT:** **Fenazaquin:** Human Health Risk Assessment for Proposed New Uses on Almonds and Cherries.

**PC Code:** 044501

**Decision No.:** 444200

**Petition No.:** 1F7825

**Risk Assessment Type:** Single Chemical/Aggregate

**TXR No.:** NA

**MRID No.:** NA

**DP Barcode:** D391819

**Registration Nos.:** 10163-295; 10163-GEE

**Regulatory Action:** Section 3 Registration

**Case No.:** NA

**CAS No.:** 120928-09-8

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. Gowan Company, LLC (Gowan) has requested a registration of new uses of fenazaquin on almonds and cherries. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of fenazaquin. A summary of the findings and an assessment of human health risk resulting from the proposed uses of fenazaquin on almonds and cherries are provided in this document. The HED team members contributing to this risk assessment include Cassi Walls (risk assessment and dietary risk assessment), Vincent Chen (hazard reevaluation), Steve Funk (residue chemistry), and Kristin Rury (occupational/residential assessments).

<b>1.0</b>	<b>Executive Summary .....</b>	<b>4</b>
<b>2.0</b>	<b>HED Recommendations .....</b>	<b>6</b>
2.1	Data Deficiencies .....	7
2.2	Tolerance Considerations .....	7
2.2.1	Enforcement Analytical Method .....	7
2.2.2	Recommended Tolerances .....	7
2.2.3	Revisions to Petitioned-For Tolerances .....	7
2.2.4	International Harmonization .....	8
2.3	Label Recommendations .....	8
<b>3.0</b>	<b>Introduction .....</b>	<b>8</b>
3.1	Chemical Identity .....	8
3.2	Physical/Chemical Characteristics .....	9
3.3	Pesticide Use Pattern .....	9
3.4	Anticipated Exposure Pathways .....	9
3.5	Consideration of Environmental Justice .....	10
<b>4.0</b>	<b>Hazard Characterization and Dose-Response Assessment .....</b>	<b>10</b>
<b>5.0</b>	<b>Dietary Exposure and Risk Assessment .....</b>	<b>17</b>
5.1	Metabolite/Degradate Residue Profile .....	17
5.1.1	Summary of Plant and Animal Metabolism Studies .....	17
5.1.2	Summary of Environmental Degradation .....	18
5.1.3	Comparison of Metabolic Pathways .....	18
5.1.4	Residues of Concern Summary and Rationale .....	19
5.2	Food Residue Profile .....	20
5.3	Water Residue Profile .....	21
5.4	Dietary Risk Assessment .....	21
5.4.1	Description of Residue Data Used in Dietary Assessment .....	21
5.4.2	Percent Crop Treated Used in Dietary Assessment .....	21
5.4.3	Acute Dietary Risk Assessment .....	21
5.4.4	Chronic Dietary Risk Assessment .....	22
5.4.5	Cancer Dietary Risk Assessment .....	22
5.4.6	Summary Table .....	22
<b>6.0</b>	<b>Residential (Non-Occupational) Exposure/Risk Characterization .....</b>	<b>23</b>
6.1	Residential Handler Exposure .....	23
6.2	Post-Application Exposure .....	23
6.3	Residential Risk Estimates for Use in Aggregate Assessment .....	23
6.4	Residential Bystander Post-application Inhalation Exposure .....	24
6.5	Spray Drift .....	24
<b>7.0</b>	<b>Aggregate Exposure/Risk Characterization .....</b>	<b>24</b>
7.1	Acute Aggregate Risk .....	24
7.2	Short-Term Aggregate Risk .....	25
7.3	Chronic Aggregate Risk .....	25
7.4	Cancer Aggregate Risk .....	25
<b>8.0</b>	<b>Cumulative Exposure/Risk Characterization .....</b>	<b>25</b>
<b>9.0</b>	<b>Occupational Exposure/Risk Characterization .....</b>	<b>26</b>
9.1	Short-Term Handler Risk .....	26
9.2	Short-/Intermediate-Term Post-Application Risk .....	28

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9.2.1	Dermal Post-application Risk.....	28
9.2.2	Inhalation Post-application Risk.....	28
10.0	References.....	29
Appendix A. Toxicology Profile.....		30
A.1	Toxicology Data Requirements.....	30
Appendix B. Proposed Metabolic Pathways for Fenazaquin (EL-436) in the Rat .....		35
Appendix C. Physical/Chemical Properties.....		36
Appendix D. Structure of Fenazaquin and its major metabolites/degradates .....		37

## 1.0 Executive Summary

### **Use Profile:**

Fenazaquin is a quinazoline-derived insecticide used to control mites and whiteflies, currently registered as an emulsifiable concentrate (EC) for use on outdoor ornamental plants, ornamental plants inside greenhouses, Christmas tree plantations, and non-bearing fruit and nut trees. There are also existing tolerances for fenazaquin on imported apples, citrus (except grapefruit), citrus oil, and pears.

The Registrant, Gowan Company, has proposed domestic uses of fenazaquin on cherries and almonds. The proposed uses will be added to the formulated end use product label (GWN-1708 F, 18.79% fenazaquin, EPA Reg. No. 10163-GEE), which is a liquid formulation containing 18.79% fenazaquin by weight and 1.6 lbs active ingredient (ai) per gallon. The product is a foliar spray applied using aerial and ground equipment at a maximum single and seasonal application rate of 0.45 lb ai/A.

### **Hazard Identification:**

The most consistently observed effects of fenazaquin exposure across species, sexes, and treatment durations were decreases in body weight, food consumption, and food efficiency. Fenazaquin was not observed to target a specific tissue. Fenazaquin is classified as “Not likely to be Carcinogenic to Humans.” There was no observed toxicity with respect to developmental toxicity, reproductive toxicity, neurotoxicity, mutagenicity, genotoxicity, or immunotoxicity. Based on the available data, toxicity endpoints and points of departure (PODs) have been selected for acute and chronic dietary, short-term incidental oral, and short- and intermediate-term inhalation exposure scenarios. A dermal assessment is not required for this chemical because there was no observed systemic toxicity in rats treated up to the limit dose (1000 mg/kg/day) and no developmental toxicity, reproductive toxicity, neurotoxicity, and immunotoxicity effects were observed in the database. The Food Quality Protection Act (FQPA) Safety Factor has been reduced to 1x because the toxicity database is complete, there is no concern for susceptibility in infants and young children, there are no neurotoxicity concerns, and there are no residual uncertainties regarding exposure.

### **Dietary Exposure (Food/Water):**

Acute: An unrefined acute dietary (food and drinking water) assessment was conducted. The assumptions of this dietary assessment included tolerance level residues for all registered and proposed crops and 100% crop treated (CT). Default processing factors were used. The surface water estimated drinking water concentration (EDWC) of 5.74 µg/L from the Tier II PRZM (Pesticide Root Zone Model) and EXAMS (EXposure Analysis Modeling System) modeling was incorporated directly into the dietary assessment.

The acute dietary (food and drinking water) exposure to fenazaquin is below HED’s level of concern [i.e., <100% of the acute Population Adjusted Dose (aPAD)] for the general U.S. population and all population subgroups. The acute dietary exposure estimates at the 95<sup>th</sup> percentile are 3% of the aPAD for the general U.S. population and 10% of the aPAD for children 1-2 years old, the most highly exposed population subgroup.

Chronic: An unrefined chronic dietary (food and drinking water) assessment was conducted. The assumptions of this dietary assessment included tolerance level residues for all registered and proposed crops and 100% crop treated (CT). Default processing factors were used. The surface water EDWC of 2.09 µg/L from the Tier II PRZM-EXAMS modeling was incorporated directly into the dietary assessment.

The chronic dietary (food and drinking water) exposure to fenazaquin is below HED's level of concern [i.e., <100% of the chronic Population Adjusted Dose (cPAD)] for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 2% of the cPAD for the general U.S. population and 10% of the cPAD for children 1-2 years old, the most highly exposed population subgroup.

### **Residential Exposure:**

There are no residential uses being requested at this time. However, the existing residential ornamental use was reassessed to incorporate revisions to the Residential Standard Operating Procedures (SOPs) and body weight assumptions.

### *Handler Exposures:*

There are no residential handler risk estimates of concern for the existing uses of fenazaquin using the Revised Residential SOPs. The level of concern (LOC) for residential handler risk estimates is a margin of exposure (MOE) of 100 (i.e., MOE < 100 are of concern). Short-term inhalation MOEs for residential handlers range from 190,000 to 19,000,000.

### *Post-application Exposures:*

A quantitative residential post-application assessment was not conducted for fenazaquin exposure for adults and children because: (1) dermal endpoints for were not selected; (2) post-application inhalation exposure is considered negligible from use on ornamentals; and (3) there is no incidental oral exposure expected from fenazaquin use on ornamental plants.

### **Aggregate Exposure:**

Acute: Aggregate acute risk is equivalent to acute dietary risk (e.g., food and drinking water exposure) where the estimates are not of concern.

Chronic: Aggregate chronic risk is equivalent to chronic dietary risk (e.g., food and drinking water exposure) where the estimates are not of concern.

Short- and Intermediate Term: There is potential short-term aggregate exposure to fenazaquin for adults from dietary exposure (which is considered background exposure) and residential dermal and inhalation exposures from handling fenazaquin. However, since no hazard was identified for the dermal route of exposure, short-term aggregate risk estimate included dietary and inhalation exposures only. The aggregate MOE for adults is 5,200 and not of concern to HED. Since there is no residential exposure for children, there is no potential short-term aggregate risk.

Intermediate-term aggregate exposures are not expected based on the use profile of fenazaquin, therefore they were not assessed.

**Occupational Exposure:***Occupational Handler Exposures:*

Occupational short- and intermediate- term dermal and inhalation exposures are expected from fenazaquin handler activities associated with the proposed almond and cherry uses. Since no hazard was identified for the dermal route of exposure, dermal exposures were not assessed. MOEs greater than 100 for the inhalation route is deemed adequate to protect occupational fenazaquin handlers. All handler scenarios resulted in MOEs greater than the level of concern (LOC = MOEs  $\geq$  100) for inhalation exposures and, therefore are not of concern.

*Occupational Post-application Exposures:*

Occupational short-term dermal exposures are expected from fenazaquin post-application activities associated with the proposed almond and cherry uses. However, since no hazard was identified for the dermal route of exposure, dermal exposures were not quantitatively assessed. Based on the Agency's current practices, a quantitative non-cancer post-application inhalation exposure assessment was not performed for fenazaquin at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for fenazaquin.

*Restricted Entry Interval:* The labeled restricted entry interval (REI) of 12-hrs is adequate to protect agricultural workers from post-application exposures to fenazaquin. Per the Worker Protection Standard (WPS), fenazaquin is classified as Toxicity Category III for acute inhalation and IV for acute dermal exposure and requires a 12-hr REI.

**Review of Human Research:**

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the PHED, AHETF, and Residential SOPs (for the garden/tree SOP); are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at <http://www.epa.gov/pesticides/science/handler-exposure-data.html> and <http://www.epa.gov/pesticides/science/post-app-exposure-data.html>.

**Environmental Justice Considerations:**

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.eh.doe.gov/oeqa/guidance/justice/eo12898.pdf>).

**2.0 HED Recommendations**

HED has examined the residue chemistry, toxicity, and exposure databases for fenazaquin and concluded that, provided a revised Section F is submitted, there are no deficiencies that would preclude granting a Section 3 registration on almonds and cherries.

## 2.1 Data Deficiencies

None

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

An acceptable analytical method exists for the enforcement of plant commodity tolerances. The HPLC-MS/MS method is the same as that used for data collection and has been shown acceptable over a range of commodities. The method has undergone successful independent laboratory confirmation. Testing with radiolabeled samples showed that the method recovers adequate amounts of the analyte.

### 2.2.2 Recommended Tolerances

Tolerances are established for residues of fenazaquin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below for plant commodities is to be determined by measuring only fenazaquin in or on the commodity.

<b>Table 2.2.2. Tolerance Summary for Fenazaquin</b>			
<b>Commodity</b>	<b>Established/Proposed Tolerance (ppm)</b>	<b>Recommended Tolerance (ppm)</b>	<b>Comments <i>Correct Commodity Definition</i></b>
Almond, hulls	0.6	4.0	A revised Section F must be submitted to propose a tolerance at 4.0 ppm
Almond	0.02	0.02	<i>Almond</i>
Cherry	1.5	2.0	A revised Section F must be submitted to propose a tolerance at 2.0 ppm.

### 2.2.3 Revisions to Petitioned-For Tolerances

The use of the Organization of Economic Cooperation and Development (OECD) tolerance derivation procedures indicates the need for the following changes in proposed tolerances: cherries from 1.5 ppm to 2.0 ppm and almond hull from 0.6 ppm to 4.0 ppm.

The tolerance expression (for plant commodities) should be stated as follows:

Tolerances are established for residues of the insecticide fenazaquin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only fenazaquin, or 4-[2-[4-(1,1-dimethylethyl)phenyl]ethoxy]quinazoline.

## 2.2.4 International Harmonization

There are no established maximum residue limits (MRLs) for fenazaquin in the Codex system. There are no established or pending MRLs in Canada for fenazaquin. Therefore, there are no harmonization issues.

## 2.3 Label Recommendations

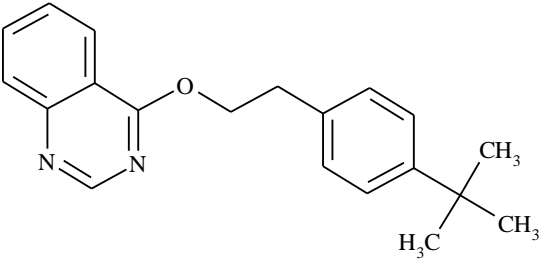
Based on discussions with the Registrant and the proposed use pattern (foliar insecticide for use in orchards on almond and cherry trees), HED recommends that language regarding chemigation application be removed from the proposed label. Fenazaquin application via chemigation should also be restricted from on the proposed label.

## 3.0 Introduction

Fenazaquin, 4-*tert*-butylphenethyl quinazolin-4-yl ether, is a quinazoline class insecticide/acaricide used to control mites and whiteflies. Fenazaquin is currently registered in the U.S. for use on Christmas trees (plantations), outdoor and greenhouse-grown ornamental plants, established ornamental landscapes (including interiorscapes and around residential premises), and on non-bearing fruit and nut trees. Additionally, fenazaquin has tolerances to support the importation of apples, pears and citrus fruits treated with fenazaquin that are grown in other countries for export to the U.S.

## 3.1 Chemical Identity

The structure and nomenclature of fenazaquin is presented below in Table 3.1. The chemical structure of fenazaquin and its major metabolites/degradates are presented in Appendix D.

Table 3.1. Fenazaquin Nomenclature.	
Compound	
Common name	Fenazaquin
Molecular weight	306.4
Company experimental names	XDE-436, EL-436, XRD-562; DE-436
IUPAC name	4- <i>tert</i> -butylphenethyl quinazolin-4-yl ether
CAS name	4-[2-[4-(1,1-dimethylethyl)phenyl]ethoxy]quinazoline
CAS registry number	120928-09-8
End-use products (EP)	10163-GEE (GWN-1708 F, 1.6 pounds ai/gal suspension concentrate)

### 3.2 Physical/Chemical Characteristics

Fenazaquin has a log octanol/water partition coefficient ( $\log K_{ow}$ ) of  $>3.0$  and is slightly water soluble indicating that it is fat soluble. However, fenazaquin has a molecular weight of 306.4 g/mol; therefore, the potential to cross biological barriers is somewhat limited. Based on laboratory and field studies, fenazaquin was found to be persistent and immobile under most environmental conditions. The vapor pressure of fenazaquin is considered low ( $1.4 \times 10^{-7}$  mm Hg at 25 °C), limiting the potential for inhalation exposure. A summary of the physical/chemical characteristics of fenazaquin is provided in Appendix C.

### 3.3 Pesticide Use Pattern

Gowan has proposed to add almond and cherry uses to the GWN-1708 F label as summarized in Table 3.3 below.

Table 3.3 Summary of Proposed Directions for Use of Fenazaquin (Label GWN-1708F, 10163-GEE).						
Application. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate lb ai/A (fl oz/A)	PHI <sup>1</sup> (days)	Use Directions and Limitations
Almonds						
Foliar spray	GWN-1708F; 10163-GEE; Suspension concentrate	0.45	1	0.45 (36)	7	Ground application in a minimum of 100 gallons water/A Aerial application in a minimum of 5 gallons water/A. Do not apply more than one application per year.
Cherries						
Foliar spray	GWN-1708F; 10163-GEE; Suspension concentrate	0.45	1	0.45 (36)	3	Ground application in a minimum of 50 gallons water/A Aerial application in a minimum of 5 gallons water/A. Do not apply more than one application per year.

<sup>1</sup> PHI = Preharvest interval

### 3.4 Anticipated Exposure Pathways

RD has requested an assessment of human health risk to support the proposed new use of fenazaquin on almonds and cherries. Humans may be exposed to fenazaquin in food and drinking water, since fenazaquin may be applied directly to growing crops and application may result in fenazaquin reaching surface and ground water sources of drinking water. There are ornamental residential uses of fenazaquin, so there are likely to be exposures in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for

post-application exposure for workers re-entering treated fields.

Risk assessments have been previously prepared for the existing uses of fenazaquin. This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of fenazaquin, but also considers the existing uses as well, particularly for the dietary exposure assessment.

### **3.5 Consideration of Environmental Justice**

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

### **4.0 Hazard Characterization and Dose-Response Assessment**

Fenazaquin is a quinazoline-derived insecticide used to control mites and whiteflies. Fenazaquin's pesticidal mode of action is through inhibition of the mitochondrial electron transport at the Complex I site (NADH-ubiquinone reductase). There are no mammalian molecular data to confirm this mode of action in the test animals.

#### **4.1 Toxicology Studies Available for Analysis**

The toxicity studies available for risk assessment include an acute toxicity battery; subchronic oral studies in rats, hamsters, and dogs; subchronic dermal study in rabbits; chronic toxicity studies in rats and dogs; carcinogenicity studies in rats and hamsters; developmental toxicity studies in rats and rabbits; a 2-generation reproduction study in rats; a battery of mutagenicity and genotoxicity studies; an acute neurotoxicity study in rats; metabolism and pharmacokinetic studies in rats; and an immunotoxicity study in rats.

Three studies, a 21-day dermal toxicity in rabbits, a developmental toxicity in rabbits, and an acute neurotoxicity study, were previously identified to have deficiencies. These studies were further evaluated in the context of the toxicity results from the entire database. The results of this evaluation were presented to HED Hazard and Science Policy Council (HASPOC). The Council conducted a thorough analysis of all the available toxicity and exposure information for fenazaquin, and recommended upgrading the classification and not requiring new studies with respect to (1) acute neurotoxicity, (2) subchronic dermal toxicity, and (3) developmental toxicity study in rabbits. The requirements for a subchronic inhalation toxicity study and a subchronic neurotoxicity study in rats were also waived (HASPOC 10 April 2014; TXR 0056942).

## 4.2 Absorption, Distribution, Metabolism and Excretion (ADME)

ADME was evaluated in rats of both sexes under the following scenarios: A single or repeated oral low dose administration (1 mg/kg); and a single oral high dose administration (30 mg/kg). Fenazaquin demonstrated rapid absorption, systemic distribution, extensive metabolism, and near complete excretion within 72 hours. Fenazaquin distribution does not correlate with organ-specific toxicity nor is it indicative of bioaccumulation potential.

Rats absorbed 65% of the orally administered dose (AD) in male rats over 48 hours. The data collected in male and non-pregnant female rats at 1 mg/kg suggests a time to peak plasma level ( $t_{max}$ ) between 4-8 hrs. The plasma elimination half-life ( $t_{1/2}$ ) could not be ascertained due to the limitations of the pharmacokinetic study's design. Fenazaquin residues were distributed in low and insubstantial levels (<0.04% AD) throughout the rat carcass. The majority of the AD was eliminated from the rat within 48 hrs (97% AD); and feces was the primary route of elimination with the parent compound accounting for 1.2-4.2% AD.

Fenazaquin was extensively metabolized in rats, and the major metabolites were AN-1 (found in urine), and the fecal metabolites F-1, F-2 and F-3 (as shown in Appendix B). Based on characterization of metabolites, metabolism was mostly the result of cleavage separating the two aromatic rings or oxidation of the *tert*-butyl group (to either a hydroxyl or carboxyl group).

### 4.2.1 Dermal Absorption

The registrant submitted an *in vitro* dermal penetration study (OECD 428), the results suggests a dermal absorption factor (DAF) of 0.5-7.3%. In the absence of an *in vivo* dermal absorption study, a definitive DAF could not be established for use in risk assessment with respect to the dermal penetration guideline (OCSPP 870.7600).

## 4.3 Toxicological Effects

The most consistently observed effects of fenazaquin exposure across species, genders, and treatment durations were decreases in body weight, food consumption, and food efficiency. The effects on body weight and food consumption were consistent with the commonly observed findings for compounds which disrupt mitochondrial respiration. Other effects noted were mild dehydration and certain clinical signs seen at relatively high dose levels in the acute neurotoxicity study. These clinical signs, which included increased foot splay, decreased motor

activity, sluggish arousal, unusual posture, abnormal gait, and altered response to auditory stimuli were seen in the absence of any neuropathological changes and were not considered to be related to neurotoxicity. In a 90-day study in hamsters, treated animals had an increased incidence of testicular hypospermatogenesis and reduced testicular and prostate weight; however, these findings were not replicated in the hamster carcinogenicity study which suggest the effects were transient or reversible.

Fenazaquin did not cause any developmental or reproductive toxicity at the doses tested in rats and rabbits. In the rat study, developmental toxicity was not observed in the presence of maternal toxicity (i.e. decreases in body weight gain, food consumption, and food efficiency). In the rabbit study, no developmental or maternal toxicity was seen. In the reproduction study, systemic toxicity manifested in parental animals as excessive salivation and decreased body weight and food intake; in offspring as decreased body weight gain; and there was no observed reproductive toxicity. Therefore, there is no developmental toxicity or reproductive susceptibility with respect to fetal and developing young animals with *in utero* and postnatal exposures.

Carcinogenicity was evaluated in the hamster instead of the mouse because the hamster was found to be more sensitive to the effects of fenazaquin than mice due to slower elimination kinetics for hamster. In a three-month feeding study in the mouse, it was found that 6-22x higher dose levels were required to elicit a comparable effect in mice than in the hamster. The results of the rat and hamster carcinogenicity studies demonstrated no increase in treatment-related tumor incidence. Therefore, fenazaquin was classified as “Not likely to be Carcinogenic to Humans.”

Fenazaquin did not cause mutagenicity, genotoxicity, neurotoxicity, or immunotoxicity. Fenazaquin did not demonstrate any systemic toxicity in a 21-day dermal toxicity study in rabbits up to the limit dose (1000 mg/kg/day).

Fenazaquin has high acute oral toxicity (Category II); and low acute toxicity by dermal and inhalation routes of exposure (Categories IV and III, respectively). Fenazaquin is not a skin irritant (Category III), but it is minimally irritating to the eye (Category IV). Fenazaquin is considered to be a dermal sensitizer; Technical Review Branch (TRB) / Registration Division (RD) made this recommendation due to the lack of an acceptable dermal sensitization study demonstrating otherwise.

#### **4.4 Safety Factor for Infants and Children (FQPA Safety Factor)**

The 10x FQPA Safety Factor can be reduced to 1x because the toxicity database is complete, there is no evidence of sensitivity/susceptibility in the developing organism, no evidence of neurotoxicity, and no residual uncertainty in the exposure data. The details are discussed below.

##### **4.4.1 Completeness of the Toxicology Database**

As described in Section 4.1, HED HASPOC recommended upgrading and not requiring new studies for acute neurotoxicity study, subchronic dermal toxicity study, and developmental study in rabbits. In addition, the HASPOC recommended waiving the requirements for a subchronic inhalation study and a subchronic neurotoxicity study. In the presence of these recommendations,

the toxicity database for fenazaquin was considered complete and sufficient for assessing susceptibility to infants and children as required by FQPA.

#### **4.4.2 Evidence of Neurotoxicity**

There are no indications in any of the studies available that the nervous system is a target for fenazaquin. In the acute neurotoxicity study in rats at the highest dose tested (130 mg/kg/day in males and 120 mg/kg/day in females), the clinical signs such as mild dehydration, increased foot splay, decreased motor activity, sluggish arousal, unusual posture, abnormal gait, and altered response to auditory stimuli were observed on Day 1 only. An increase in the incidence of minimal nerve fiber degeneration was also reported in the high dose males, but in females, this incidence was greater in controls than that in the high dose group. Considering the findings in both genders, the finding of minimal nerve fiber degeneration was considered to be equivocal because when the data for both sexes are combined the incidence for the high dose animals was no different from the controls. The neuropathology findings seen in this study were also evaluated by EPA's Office of Research and Development (ORD); the conclusion was that minimal nerve fiber degeneration found in the highest dose animal in this study should not be considered as a treatment-related effect for the reasons just discussed. Therefore, in the absence of neuropathology, the observed clinical signs were not considered to be related to neurotoxicity. Additional supporting evidence for this conclusion was that in the repeated dosing studies in rats, dogs, and hamsters, there were no clinical signs indicative of neurotoxicity; no gross/microscopic pathology findings were observed in central or peripheral nervous systems in these studies.

The HASPOC evaluated the available toxicity data in association with the possible need for a subchronic neurotoxicity study, and it was determined that a subchronic neurotoxicity study was not needed at this time because 1) indications of treatment-related clinical signs in the ACN were well-characterized; 2) effects seen in ACN were observed at doses higher than current PODs; and 3) there was no indication of treatment-related neurotoxicity observed in any repeated dosing studies. In the absence of gross neurotoxicity or neuropathology findings in the available database, a developmental neurotoxicity study is not required.

#### **4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal**

Susceptibility/sensitivity in the developing animals was evaluated in developmental toxicity studies in rats and rabbits as well as a reproduction and fertility study in rats.

In the rabbit developmental toxicity study, toxicity was not observed in dams or fetuses up to 13 mg/kg/day; HED excluded the high dose group (60 mg/kg/day) because of a loss of nearly a third of that dose group due to technical difficulties that were not deemed to be test substance related. Despite the technical difficulties, the surviving animals at the 60 mg/kg/day dose group did not demonstrate any maternal or fetal toxicity. Additionally, there were no fetal effects up to the highest dose tested (100 mg/kg/day) in a range-finding developmental toxicity study in rabbits. In the rat developmental toxicity study at the highest dose tested (40 mg/kg/day), maternal toxicity consisting of decreases in food consumption and body weight gain occurred in the absence of any developmental toxicity in fetuses.

In the reproduction study, the offspring effects (i.e., decreased body weight gain during lactation) occurred only in the presence of parental toxicity (i.e., excessive salivation and decreased body weight, body weight gain, and food intake). Therefore, there is no evidence of sensitivity/susceptibility in the developing or young animal. Clear NOAELs and LOAELs are available for all the parental and offspring effects. Therefore, there are no residual pre- or post-natal concerns.

#### **4.4.4 Residual Uncertainty in the Exposure Database**

There are no residual uncertainties in the exposure database. Since the dietary and non-dietary exposure estimates were based on several conservative assumptions, HED does not believe that the exposure estimates are underestimated. The acute and chronic dietary assessments conducted with DEEM-FCID were screening level analyses. The assessments utilized tolerance values, default processing factors, and assumed that 100% of the registered and proposed crops were treated with fenazaquin. The dietary exposure analyses also assumed that all drinking water will contain fenazaquin at the highest EDWC levels modeled by Environmental Fate and Effects Division (EFED). Therefore, the dietary exposure analyses do not underestimate risk from acute or chronic dietary exposure to fenazaquin. Similarly, HED does not believe that the non-dietary residential exposures are not underestimated because they are also based on conservative assumptions, including maximum application rates, and standard values for unit exposures, amount handled as described in the Residential SOPs.

### **4.5 Toxicity Endpoint and Point of Departure Selection**

#### **4.5.1 Dose-Response Assessment**

The doses and endpoints selected for dietary risk assessments are shown in Table 4.5.4.1. For acute dietary exposure, the results from the immunotoxicity study were considered in selecting toxicity endpoints and points of departure (POD) for risk assessment. The NOAEL of 15 mg/kg/day was selected as the POD based on clinical signs (i.e. general ataxia/hypoactivity) observed after a single exposure at the LOAEL of 30 mg/kg/day. The endpoint is appropriate for this exposure scenario since the effects were seen after a single oral administration. In addition, it is also protective of the clinical signs (i.e., mild dehydration) seen in the acute neurotoxicity study at 60 mg/kg (LOAEL). An acute reference dose (aRfD) of 0.15 mg/kg/day was derived from the NOAEL with the application of an Uncertainty Factor (UF) of 100x (10x inter-species extrapolation, 10x intra-species variations factor).

A separate endpoint of concern for pregnant females (13-49 years of age) was not selected since no endpoints attributable to a single dose were identified in the developmental toxicity studies in rats and rabbits.

For chronic dietary exposure, the toxicity endpoints of decreases in body weight, food consumption, and food efficiency were selected, and these effects were seen at similar dose levels in both subchronic (15 mg/kg/day) and chronic (12 mg/kg/day) oral toxicity studies in dogs. The NOAELs were the same for both chronic and subchronic toxicity studies in dogs. The results from these two studies demonstrated no increase in severity with increased treatment

durations. Hence, the subchronic and chronic toxicity studies in dogs were appropriate to be employed as co-critical studies for toxicity end point and point of departure selections for the chronic exposure scenario. A chronic reference dose (cRfD) of 0.05 mg/kg/day was derived from a NOAEL of 5 mg/kg/day and an UF of 100x. While the NOAEL of the chronic toxicity study in the hamster (2 mg/kg/day) is lower than that of dogs, it was not selected because it was considered to be an artifact of dose-selection.

For the short term incidental oral exposure risk assessment, the toxicity endpoints and NOAEL seen in the subchronic and chronic dog studies were deemed appropriate for the short term incidental oral exposure scenario since the effects in the dog studies were similar in both subchronic and chronic toxicity studies. Similar effects were also seen in the reproduction study.

Dermal endpoints for both short- and intermediate-term exposures were not selected because an *in vitro* dermal penetration study suggested that the dermal absorption was less than 8%, and there were no systemic effects observed in the 21-day dermal toxicity study in rabbits up to the limit dose (1000 mg/kg/day). There was no treatment related toxic effects observed in the oral studies with respect to developmental and reproductive toxicity or susceptibility; additionally, no toxic effects were observed with respect to neurotoxicity or immunotoxicity.

An inhalation study is not included in the available database (and the requirement has been waived as discussed in Section 4.1) so inhalation endpoints for occupational and residential exposures were derived from oral studies. For short- and intermediate-term inhalation, the NOAEL of 5 mg/kg/day was used as the POD from co-critical subchronic and chronic toxicity studies in dogs, with LOAELs of 15 and 12 mg/kg/day, respectively, based on decreased body weight and food consumption/efficiency.

There are no long-term dermal or inhalation scenarios anticipated for this risk assessment

#### **4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment**

HED has considered the potential for concurrent exposure via oral, dermal, and inhalation routes; HED aggregates exposure from different routes for each population if the same toxic effects are seen for that duration of exposure by each route. Since oral and inhalation endpoints are based on the same effects (i.e., decreases in body weight, food consumption, and food efficiency), these routes of exposure may be combined for residential exposure risk assessment.

#### **4.5.3 Cancer Classification and Risk Assessment Recommendation**

Fenazaquin is classified as “*Not likely to be Carcinogenic to Humans*” based on the absence of a treatment-related increase in tumor incidence in adequately conducted carcinogenicity studies in hamsters and rats.

#### 4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 presents a summary of the endpoints selected for fenazaquin for use in risk assessments. A summary of the acute toxicity categories for the technical material are included in Appendix A.

<b>Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for use in Dietary and Non-Occupational Human Health Risk Assessments</b>				
<b>Exposure Scenario</b>	<b>Point of Departure (POD)</b>	<b>Uncertainty / FQPA Safety Factors</b>	<b>RfD, PAD, and LOC for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Acute Dietary General population (including infants and children) And Females (13-49 years)	NOAEL = 15 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	aRfD = 0.15 mg/kg/day  aPAD = 0.15 mg/kg/day	<u>Immunotoxicity – Rat</u> LOAEL = 30 mg/kg/day Based on clinical signs (general ataxia/hypoactivity) observed in 1 animal on Day 02 and 3 animals on Day 03 of dosing.
Chronic Dietary All populations	NOAEL = 5 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	cRfD = 0.05 mg/kg/day  cPAD = 0.05 mg/kg/day	<u>Co-Critical: Subchronic and Chronic Toxicity – Dog</u>  <u>Subchronic Toxicity – Dog</u> LOAEL = 15 mg/kg/day Based on decreased body weight and food consumption/efficiency.  <u>Chronic Toxicity – Dog</u> LOAEL = 12 mg/kg/day Based on decreased body weight and food consumption/efficiency
Incidental Oral Short Term (1-30 days)	NOAEL = 5 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	LOC = MOE = 100	<u>Co-Critical: Subchronic and Chronic Toxicity – Dog</u>  Same as Chronic Dietary
Inhalation Short Term (1-30 days) And Intermediate Term (1-6 months)	NOAEL = 5 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF =	LOC = MOE = 100	<u>Co-Critical: Subchronic and Chronic Toxicity – Dog</u>  Same as Chronic Dietary
Dermal Short Term (1-30 days) And Intermediate Term (1-6 months)	There is no identified hazard for this scenario because there was no observed systemic toxicity in rats treated up to the limit dose (1000 mg/kg/day). Additionally, developmental toxicity, reproductive susceptibility, neurotoxicity, and immunotoxicity effects were not observed in the database.			
Cancer (oral, dermal, and inhalation)	Classification: “Not likely to be Carcinogenic to Humans” based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

<b>Table 4.5.4.2: Summary of Toxicological Doses and Endpoints for use in Occupational Human Health Risk Assessments</b>				
<b>Exposure Scenario</b>	<b>Point of Departure (POD)</b>	<b>Uncertainty / FQPA Safety Factors</b>	<b>RfD, PAD, and LOC for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Inhalation Short Term (1-30 days) And Intermediate Term (1-6 months)	NOAEL = 5 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x	LOC = MOE = 100	<u>Co-Critical: Subchronic and Chronic Toxicity – Dog</u>  Same as Chronic Dietary exposure scenario in Table 4.5.4.1
Dermal Short Term (1-30 days) And Intermediate Term (1-6 months)	There is no identified hazard for this scenario because there was no observed systemic toxicity in rats treated up to the limit dose (1000 mg/kg/day). Additionally, developmental toxicity, reproductive susceptibility, neurotoxicity, and immunotoxicity effects were not observed in the database.			
Cancer (oral, dermal, and inhalation)	Classification: “Not likely to be Carcinogenic to Humans” based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Animal Metabolism Studies

Metabolism studies in apples and citrus were previously evaluated to support tolerances in/on imported apple, citrus fruits (except grapefruit), and pear. New metabolism studies conducted with grapes and corn; lettuce, wheat and radish (confined rotational); poultry and goat. An aerobic soil metabolism study and aerobic aquatic metabolism study were submitted to support the proposed new uses. It should be noted that subsequent to the completion of the residue chemistry memo (D391810, S. Funk, 07/25/12) and ROCKS meeting decision (D397773, I. Negrón-Encarnación, 04/18/12) Gowan amended the proposed label to include only almonds and cherries. There is one livestock (cattle) feed item, almond hulls, however, based on a maximum reasonably based diet (MRBD), no residues are anticipated in the livestock commodities.

The residue chemistry database is adequate for determining residues of concern. Metabolism studies were conducted with fenazaquin radiolabeled in the phenyl ring or in the quinazoline ring. Parent fenazaquin is a major residue in corn grain, corn stover, grape, orange, and apple. Fenazaquin dimer, a photolysis product, is absent in grapes, but is a major metabolite in corn stover and apple, and a minor metabolite in corn grain. Other metabolites are generally <10% of the Total Radioactive Residue (TRR) across all matrices and PHIs. The exceptions are metabolite I (2-hydroxy fenazaquin) and metabolite C (fenazaquin alcohol) which were observed in grapes at maximum concentrations of 26% and 12.9 % of the TRR, respectively. However, about half of metabolite I is conjugated. See Appendix D for a list and description of all metabolites.

A confined rotational crop study (1X) was conducted with lettuce, wheat, and radish. Fenazaquin was found at concentrations  $\geq 0.01$  ppm only in 30-day PBI radish root (0.03 ppm). Fenazaquin was extensively degraded/metabolized in the confined rotational crop study to multiple metabolites/degradates that were also observed in the primary crop metabolism studies. With a 120-day plant back interval (PBI) for root and tuber and bulb vegetables (and 30 days for all other crops), there will be no significant rotational crop residues.

The livestock metabolism studies were performed by administering radiolabeled fenazaquin to poultry and goats. The highest total radioactive residues (TRR) were in the fat and liver of goats and the fat of poultry, suggesting that fenazaquin partitions into fat and is detoxified via the liver in ruminants. In addition, fenazaquin was a major residue in milk. Fenazaquin was absent in goat muscle, kidney, and liver and was present at low levels ( $<10\%$  TRR or  $<0.01$  ppm) in poultry muscle and eggs and absent in liver. Major metabolites in goat were metabolite M29 in muscle, kidney, and liver; metabolite M34 in liver; and metabolite J in milk. Metabolite J in milk was at a low absolute amount,  $<0.01$  ppm. The major metabolite in muscle, liver, and eggs of poultry was metabolite I.

### 5.1.2 Summary of Environmental Degradation

Fenazaquin is persistent and immobile in terrestrial and aquatic environments. Degradation products of fenazaquin can be classified according to their formation by cleavage of the ether (ethoxy) linkage. This cleavage generates products with only the *tert*-butylphenyl group or the quinazoline group. The quinazoline products form mostly 4-quinazolinol and 2,4-quinazoline-diol. Linkage intact products are reactions involving the quinazoline part of the molecule. Major degradation products ( $> 10\%$  of applied radioactivity) of fenazaquin are 4-(2-(4-(1,1-dimethylethyl)phenyl)ethoxy)quinazolinone (Metabolite 1), and 2-Methyl-2-(4-{2-[(2-oxo-1,2-dihydroquinazolin-4-yl)oxy]ethyl}phenyl) propanoic acid (Metabolite 29).

The environmental fate studies showed that fenazaquin has a half-life from 51 to 123.8 days in aerobic soil and 58.7 to 133.3 days in aerobic aquatic environments. Two major degradates were identified in the aerobic aquatic metabolism, metabolite 1 and metabolite 29. The half-life of fenazaquin total toxic residues (parent + metabolite 1 + metabolite 29) ranged from 73 to 197 days in aerobic soil metabolism studies, and 65 to 291 days in aerobic aquatic environments. Additionally, the mobility of the metabolites, especially Metabolite 29, is expected to be higher than parent fenazaquin.

### 5.1.3 Comparison of Metabolic Pathways

Fenazaquin is extensively metabolized in rats, resulting with the major metabolites of AN-1 (found in urine) and the fecal metabolites (F-1, F-2 and F-3) (see Appendix B). Based on characterization of metabolites, metabolism was mostly the result of cleavage separating the two aromatic rings or oxidation of the *tert*-butyl group (to either a hydroxyl or carboxyl group).

The predominant residues in plants are parent fenazaquin and its dimer, which is a photolysis product. The dimer is unlikely to be cleaved back to the parent. Fenazaquin tends to be a

surface residue and metabolizes via oxidation of the *t*-butyl methyl group, oxidation of the C-2 of the quinazoline ring, and hydroxylation/cleavage of the ether linkage.

The aquatic metabolism studies showed metabolite 1 and metabolite 29 as major metabolites. Metabolites are formed via cleavage of the ether linkage.

#### 5.1.4 Residues of Concern Summary and Rationale

The residue of concern for risk assessment and tolerance enforcement in primary and rotational crops is parent fenazaquin. Parent fenazaquin, metabolite 1 and metabolite M29 are included as residues of concern in drinking water. Table 5.1.4 summarized the residues of concern for fenazaquin.

*Plants:* The predominant residues in plants are parent fenazaquin and its dimer. The dimer is excluded as a residue of concern since it is unlikely to be cleaved back to the parent, and is not likely to be bioavailable after ingestion due to its high molecular weight and lipophilic properties. Metabolite I was not considered a residue of concern, since about half of it is conjugated and it was observed in grapes 76 days after treatment (DAT), which is much longer than the proposed PHI of 7 days. Although metabolite C was 12.9% of the TRR in grapes 49 DAT, the absolute amount (0.046 ppm) is fairly low. Metabolite C was absent or <10% TRR in other crops studied. Therefore, it is not considered a residue of concern. The residue of concern for risk assessment and tolerance enforcement in primary crops is parent fenazaquin.

*Rotational Crops:* The confined rotational crop studies showed similar results to those of primary crops. The residue of concern for risk assessment and tolerance enforcement in rotational crops is parent fenazaquin.

*Livestock:* Metabolism studies in goat showed parent fenazaquin and metabolite J as the major metabolites observed in milk. The latter was identified as 4-hydroxyquinazoline (metabolite J), which doesn't appear to be more toxic than parent fenazaquin. In addition, the absolute amount of metabolite J is below 0.01 ppm. Fenazaquin was the major component of the residue in fat, with no single metabolite identified above 1.1% TRR. Based on this, the residue of concern for risk assessment and tolerance enforcement in fat and milk of ruminants is parent fenazaquin. Two different major metabolites were observed in meat, liver and/or kidney, metabolite M29 and metabolite M34. The latter is excluded as a residue of concern since it was only observed as a major metabolite in goat liver (15.3% TRR) and it appears to be very water soluble. The residue of concern for risk assessment and tolerance enforcement in kidney, liver and muscle of ruminant is parent fenazaquin and metabolite M29. Based on the proposed uses of fenazaquin, there is no reasonable expectation of residues in poultry; however, the residues of concern were identified in case new uses are proposed. Parent fenazaquin and metabolite I were the major residues observed in poultry. Both are recommended as residues of concern in poultry commodities for tolerance enforcement and risk assessment.

*Water:* The aquatic metabolism studies showed metabolite 1 and metabolite 29 as major metabolites. These are structurally similar to parent fenazaquin; therefore, they are not likely to be less toxic than the parent. The ROCKS recommends that parent fenazaquin, metabolite 1 and

metabolite M29 are included as residues of concern in drinking water. For the risk assessment, it is assumed that the M29 and metabolite 1 have a similar toxicity to the parent. Drinking water exposure is estimated for total residues of fenazaquin, M29 and metabolite 1.

<b>Table 5.1.4. Summary of Metabolites and Environmental Transformation Products to be Included in the Risk Assessment and Tolerance Expression<sup>1</sup></b>			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Fenazaquin	Fenazaquin
	Rotational Crop	Fenazaquin	Fenazaquin
Livestock	Ruminant	<i>Milk, Fat:</i> Fenazaquin <i>Liver, Kidney, Meat:</i> Fenazaquin and Metabolite M29	<i>Milk, Fat:</i> Fenazaquin <i>Liver, Kidney, Meat:</i> Fenazaquin and Metabolite M29
	Poultry	Fenazaquin and Metabolite I	Fenazaquin and Metabolite I
Drinking Water		Fenazaquin, Metabolite 29 and Metabolite 1	Not Applicable

<sup>1</sup> Fenazaquin is 4-[[4-(1,1-dimethylethyl)phenyl]ethoxy]quinazoline; Metabolite M29 is 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid and its tautomer 2-Methyl-2-(4-{2-[(2-oxo-1,2-dihydroquinazolin-4-yl)oxy]ethyl}phenyl)propanoic acid; Metabolite I is quinazoline-2,4-diol and its tautomer quinazoline-2,4(1*H*,3*H*)-dione; Metabolite 1 is 4-[2-(4-*tert*-butyl-phenyl)-ethoxy]-quinazolin-2-ol and its tautomer 4-[2-(4-*tert*-butylphenyl)ethoxy]quinazolin-2(1*H*)-one.

## 5.2 Food Residue Profile

The submitted magnitude of the residue data, summarized in Table 5.2.1, are adequate for risk assessment and tolerance assessment (D391810, S. Funk, 07/25/12). Residues of fenazaquin were detected at low levels, indicating that there will be low exposure to fenazaquin in food. Processing studies were not conducted for processed commodities associated with proposed crops.

Table 5.2.1. Summary of Residues from Field Trials with Fenazaquin											
Crop Matrix	Analyte	Applic. Rate (lb ai/acre)	PHI (days)	n <sup>1</sup>	Residues (ppm)						
					Min. <sup>2</sup>	Max. <sup>2</sup>	LAFT <sup>3</sup>	HAFT <sup>3</sup>	Median <sup>3</sup>	Mean <sup>3</sup>	SD <sup>3</sup>
STONE FRUIT, Proposed Cherry Use = 0.45 lb ai/acre total application rate, 3-day PHI											
Cherry, sweet/tart	Fenazaquin	0.45	3	12	0.233	0.965	0.255	0.914	0.521	0.587	0.246
Cherry, sweet/tart	Dimer	0.45	3	12	<0.01	0.0165	0.01	0.0163	0.01	0.0105	0.0018
TREE NUTS, Proposed Almond Use = 0.45 lb ai/acre total application rate, 7-day PHI											
Almond Nutmeat	Fenazaquin	0.44 – 0.45	7	10	<0.01	0.0116	0.01	0.011	0.010	0.010	0.0004
Almond Nutmeat	Dimer	0.44 – 0.45	7	10	<0.01	0.0360	0.01	0.0356	0.01	0.015	0.0114
Almond Hull	Fenazaquin	0.44 – 0.45	7	10	0.2174	1.674	0.27	1.47	1.2	0.94	0.567
Almond Hull	Dimer	0.44 – 0.45	7	10	<0.01	0.1647	0.015	0.154	0.034	0.0578	0.0574

<sup>1</sup> Number of samples, typically 2X number of trials.

<sup>2</sup> Values based replicates and not averages.

<sup>3</sup> Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values < LOQ (0.01 ppm) are assumed to be at the LOQ.

### 5.3 Water Residue Profile

Estimated surface water and groundwater concentrations were provided by EFED (D394030, J. Hetrick, 03/08/12) and are shown in Table 5.3. The dietary exposure assessment used the peak concentration values of 5.74 ppb for acute and 2.09 ppb for chronic assessments. The drinking water assessment is based PRZM and EXAMS modeling for all currently registered and proposed fenazaquin uses. All Tier II surface water modeling was corrected for default percent cropped area (PCA) of 0.87.

The drinking water assessment was conducted using the total toxic residue (TTR) approach. The residues considered in this assessment include fenazaquin (parent), Metabolite 1, and Metabolite 29.

Table 5.3. Summary of Estimated Surface Water and Groundwater Concentrations for Fenazaquin		
Scenario	Surface Water Conc., ppb <sup>a</sup>	Groundwater Conc., ppb <sup>b</sup>
Acute	5.74	0.704
Chronic (non-cancer)	2.09	
Chronic (cancer)	1.33	
<sup>a</sup> From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on MI cherry scenario <sup>b</sup> From the SCI-GROW model. It should be noted that based on personal communication with EFED, the PRZM-GW modeling would not produce EWDCs higher than those presented here (email from D. Spatz to C. Olinger 5/19/14)		

### 5.4 Dietary Risk Assessment

#### 5.4.1 Description of Residue Data Used in Dietary Assessment

The acute and chronic dietary analysis for non-cancer risk assessment assumed tolerance level residues for all registered and proposed crops. Default processing factors were used for all processed commodities.

#### 5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic dietary analyses assumed that 100% of the crop was treated (100% CT).

#### 5.4.3 Acute Dietary Risk Assessment

An unrefined acute dietary assessment was conducted. The assumptions of this dietary assessment included tolerance level residues for all proposed and registered crops, default processing factors, and 100% CT was assumed. A tier II (PRZM-EXAMS) EDWC derived through EFED modeling which is unlikely to underestimate the concentration of fenazaquin in

drinking water was utilized. The surface water EDWC (5.74  $\mu\text{g/L}$ ) was incorporated directly into the dietary assessment (D394030, J. Hetrick, 03/08/12).

As shown in Table 5.4.6, the acute dietary (food and drinking water) exposure to fenazaquin is below HED's level of concern [i.e., <100% of the acute Population Adjusted Dose (aPAD)] for the general U.S. population and all population subgroups. The acute dietary exposure estimates at the 95<sup>th</sup> percentile are 3% of the aPAD for the general U.S. population and 10% of the aPAD for children 1-2 years of age, the most highly exposed population subgroup.

#### 5.4.4 Chronic Dietary Risk Assessment

An unrefined chronic dietary assessment was conducted. Tolerance level residues, 100% CT, and default processing factors were used to determine the chronic dietary exposure and risk estimates. A tier II EDWC derived through EFED modeling which is unlikely to underestimate the concentration of fenazaquin in drinking water was utilized. The ground water EDWC (2.09  $\mu\text{g/L}$ ) was incorporated directly into the dietary assessment (D394030, J. Hetrick, 03/08/12). As shown in Table 5.4.6, the chronic dietary (food and drinking water) exposure to fenazaquin is below HED's level of concern (<100% cPAD) for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 2% of the cPAD for the general U.S. population and 10% of the cPAD for children 1-2 years of age, the most highly exposed population subgroup.

#### 5.4.5 Cancer Dietary Risk Assessment

A cancer dietary risk assessment was not conducted because there was no evidence of carcinogenicity to humans based on lack of carcinogenic effects in the rat and mouse carcinogenicity studies.

#### 5.4.6 Summary Table

<b>Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure Analysis for Fenazaquin Using DEEM-FCID</b>				
<b>Population Subgroup</b>	<b>Acute Dietary (95<sup>th</sup> Percentile)</b>		<b>Chronic Dietary</b>	
	<b>Dietary Exposure (mg/kg/day)</b>	<b>% aPAD</b>	<b>Dietary Exposure (mg/kg/day)</b>	<b>% cPAD</b>
General U.S. Population	0.004348	3	0.000949	2
All Infants (< 1 year old)	0.007455	5	0.001831	4
<b>Children 1-2 years old</b>	<b>0.015404</b>	<b>10</b>	<b>0.004753</b>	<b>10</b>
Children 3-5 years old	0.011604	8	0.003358	7
Children 6-12 years old	0.006134	4	0.001481	3
Youth 13-19 years old	0.003965	3	0.000777	2
Adults 20-49 years old	0.002985	2	0.000586	1
Adults 50-99 years old	0.002568	2	0.000619	1
Females 13-49 years old	0.003034	2	0.000613	1

\*The subpopulation with the highest risk estimates

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no residential uses being requested at this time. However, there are existing residential uses that were reassessed using the updates to the 2012 HED Residential SOPs.

### 6.1 Residential Handler Exposure

There are existing residential ornamental uses that were reassessed using the updates to the 2012 HED Residential SOPs. It is assumed that most residential uses will result in short-term (1-30 day) exposures. Residential handlers are assumed to be wearing short-sleeved shirts, short pants, shoes, and socks while handling fenazaquin. Because there was no dermal endpoint chosen for fenazaquin, risk from exposure to fenazaquin was assessed for the inhalation route only. Table 6.1 lists the residential handler inhalation risk estimates for ornamental treatments. Residential handler inhalation MOEs were not of concern to HED, and ranged from 190,000 to 19,000,000.

Table 6.1: Residential Handler Non-cancer Exposure and Risk Estimates for Fenazaquin.						
Exposure Scenario	Level of Concern	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate <sup>1</sup>	Amount Handled Daily <sup>2</sup>	Inhalation	
					Dose (mg/kg/day) <sup>3</sup>	MOE <sup>4</sup>
Mixer/Loader/Applicator to Ornamentals						
Manually Pressurized Handwand	100	0.018	0.003 lb ai/gal	5 gal	0.0000034	1,500,000
Hose-End Sprayer		0.0014		11 gal	0.00000058	8.700,000
Backpack Sprayer		0.14		5 gal	0.000026	190,000
Sprinkler Can		0.0014		5 gal	0.00000026	19,000,000

1 Based on registered label (EPA Reg. No. 10163-297).

2 Based on HED's 2012 Residential SOPs (<http://www.epa.gov/pesticides/science/residential-exposure-sop.html>).

3 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Amount Handled (gallons/day) ÷ BW (80 kg).

4 Inhalation MOE = Inhalation NOAEL (5 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

### 6.2 Post-Application Exposure

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with fenazaquin. However, since there is no adverse systemic hazard via the dermal route of exposure, and there is no incidental oral exposure expected from fenazaquin use on ornamental plants, a residential post-application assessment has not been conducted.

### 6.3 Residential Risk Estimates for Use in Aggregate Assessment

The recommended residential exposure for use in the adult aggregate assessment reflects inhalation exposure from applications to ornamentals via backpack sprayer (0.000026 mg/kg/day). Since there is no residential incidental oral exposure expected for children 1<2 years old on ornamental plants, the aggregate assessment for children will only include exposure from food and water.

## 6.4 Residential Bystander Post-application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (<http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html>). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>).

During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for fenazaquin.

## 6.5 Spray Drift

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for fenazaquin. The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information).<sup>1</sup> The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift*. This document outlines the quantification of indirect non-occupational exposure to drift.

## 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

### 7.1 Acute Aggregate Risk

The acute aggregate risk is equal to the acute dietary (food and drinking water) exposure. Refer to Section 5.4.3.

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<sup>1</sup> Available: <http://www.epa.gov/opp00001/factsheets/spraydrift.htm>

## 7.2 Short-Term Aggregate Risk

There is potential short-term exposure to fenazaquin via the dietary pathway (which is considered background exposure) and the residential pathway (which is considered the primary pathway). Since intermediate-term residential exposures are not likely to occur, intermediate-term aggregate risks were not assessed. The short-term aggregate exposure assessment for adults includes dietary (food and drinking water) and inhalation handler exposures. The most conservative scenario was chosen. Since there is no residential incidental oral exposure expected for children 1<2 years old on ornamental plants, the aggregate assessment for children will only include exposure from food and water. For a description of the residential exposure scenarios considered in the aggregate assessment, see Section 6.1.

Table 7.2 Short-Term Aggregate Risk Calculations							
Population	Short-Term Scenario						
	NOAEL mg/kg/day	LOC <sup>1</sup>	Max Allowable Exposure <sup>2</sup> mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day <sup>3</sup>	Total Exposure mg/kg/day <sup>4</sup>	Aggregate MOE (food, water, and residential) <sup>5</sup>
Adult Male	5	100	0.05	0.000949	0.000026	0.000975	5,200

<sup>1</sup> LOC = standard inter- and intra- species uncertainty factors totaling 100

<sup>2</sup> Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC

<sup>3</sup> Residential Exposure = Inhalation Handler Exposure. Table 6.1.

<sup>4</sup> Total Exposure = Avg Food & Water Exposure + Residential Exposure

<sup>5</sup> Aggregate MOE = [NOAEL ÷ (Avg Food & Water Exposure + Residential Exposure)]

## 7.3 Chronic Aggregate Risk

The chronic aggregate risk is equal to the chronic dietary (food and drinking water) exposure. Refer to Section 5.4.4.

## 7.4 Cancer Aggregate Risk

A cancer aggregate risk assessment was not conducted because there was no evidence of carcinogenicity to humans based on lack of carcinogenic effects in the rat and mouse carcinogenicity studies.

## 8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fenazaquin and any other substances and fenazaquin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fenazaquin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common

mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

## **9.0 Occupational Exposure/Risk Characterization**

### **9.1 Short-Term Handler Risk**

Occupational exposures are expected to occur from the proposed fenazaquin use on almonds and cherries. Only short-term (1-30 consecutive days) dermal and inhalation exposures are expected because fenazaquin has been proposed for use only once per season. Additionally, for inhalation exposures, the POD selected are considered protective of both short- and intermediate-term durations. Dermal risks were not assessed since a dermal hazard was not identified.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/Loading liquid formulation for aerial, airblast, and application;
- Applying sprays with aerial, airblast, and handheld equipment;
- Flagging for aerial applications; and
- Mixing/Loading/Applying sprays using mechanically pressurized handgun.

Results are presented for "baseline," defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). Fenazaquin applicators and other handlers must wear long-sleeved shirts, long pants, chemical resistant gloves, shoes, and socks. For those mixing/loading/applying with a high-pressure handwand, coveralls must also be worn.

Short- and intermediate-term risk estimates for occupational handlers are included in Table 9.1.1. All handler scenarios resulted in MOEs greater than the LOC ( $\text{MOEs} \geq 100$ ) for baseline inhalation exposures, and therefore are not of concern. The short-term occupational handler inhalation MOEs ranged from 4,700 to 520,000.

**Table 9.1.1: Occupational Handler Non-Cancer Exposure and Risk Estimates for Fenazaquin.**

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai) <sup>1</sup>	Maximum Application Rate <sup>2</sup>	Area Treated or Amount Handled Daily <sup>3</sup>	Inhalation	
			Baseline (no respirator)			Dose (mg/kg/day) <sup>4</sup>	MOE <sup>5</sup>
Mixer/Loader							
Mixing/Loading Liquids for Aerial Application	Almonds and Cherries	100	0.219	0.45 lb ai/A	350 acres	0.00043	12,000
Mixing/Loading Liquids for Airblast Application					40 acres	0.000049	100,000
Applicator							
Aerial Application	Almonds and Cherries	100	0.0049	0.45 lb ai/A	350 acres	0.0000097	520,000
Airblast Application			4.71		40 acres	0.0011	4,700
Flagger							
Flagging for Aerial Application	Almonds and Cherries	100	0.35	0.45 lb ai/A	350 acres	0.00069	7,300
Mixer/Loader/Applicator							
Mixing/Loading/Applying using Mechanically Pressurized Handgun	Almonds and Cherries	100	3.9	0.0090 lb ai/gal	1000 gal	0.00044	11,000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2014); Level of mitigation: Baseline, except for aerial application which is baseline with Eng. Controls.

2 Based on proposed label (Reg. No. 10163-GEE).

3 Exposure Science Advisory Council Policy #9.1.

4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).

5 Inhalation MOE = Inhalation NOAEL (5 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## **9.2 Short-/Intermediate-Term Post-Application Risk**

### **9.2.1 Dermal Post-application Risk**

There is the potential for occupational dermal post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with fenazaquin. However, since there is no adverse systemic hazard via the dermal route of exposure, an occupational post-application assessment has not been conducted.

#### Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of fenazaquin. Fenazaquin is classified as Toxicity Category IV via the dermal route and Toxicity Category IV for skin irritation potential. It is classified as a skin sensitizer. Under 40 CFR 156.208(c)(2)(iii), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to fenazaquin.

### **9.2.2 Inhalation Post-application Risk**

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (<http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html>). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for fenazaquin.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

Furthermore, inhalation exposure during dusty mechanical activities such as shaking and mechanical harvesting is another potential source of post-application inhalation exposure. However, the airblast applicator scenario is believed to represent a reasonable worst case surrogate estimate of post-application inhalation exposure during these dusty mechanical harvesting activities. The non-cancer inhalation risk estimate for commercial airblast application is not of concern (i.e., MOE > 100).

## 10.0 References

Funk, S., 07/25/12, DP381810, 401360, *Fenazaquin. Petition for the Establishment of Permanent Tolerances and Registration for Use on Alfalfa, Avocado, Berry Fruit Group 13, Citrus Fruits Group 10, Field Corn, Sweet Corn, Cotton, Cucurbit Vegetables Group 9, Edible-Podded Legume Vegetables Subgroup 6-A, Succulent Shelled Pea and Bean Subgroup 6B (Except Soybean), Dry Bean and Pea Subgroup 6-C, Fruiting Vegetables (Except Cucurbits) Group 8, Grapes, Hops, Mint, Pome Fruits Group 11, Stone Fruits Group 12, Strawberry, and Tree Nuts Group 14. Summary of Analytical Chemistry and Residue Data.*

Hebert, J., DP394030, 03/8/12, *Drinking Water Assessment to Support First Fenazaquin (4-tert-butylphenethyl quinazolin-4-yl ether) Use on Food Crops.*

Negrón-Encarnación, I., 04/18/12, DP397773, *Fenazaquin. Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS).*

Rury, K., 08/XX/14, DP391813, *FENAZAQUIN: Occupational Exposure Assessment for Proposed Use on Almonds and Cherries, and a Re-Evaluation of Existing Residential Uses.*

Walls, C., 06/16/14, DP391808, *Fenazaquin: Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Section 3 Registration Action on Almonds and Cherries.*

## Appendix A. Toxicology Profile

### A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food uses are in the table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

<b>Table A.1: Toxicology Data Requirements</b>				
<b>Guideline</b>	<b>Study Type</b>	<b>Required</b>	<b>Submitted</b>	<b>Satisfied</b>
870.1100	Acute Oral Toxicity	Yes	Yes	Yes
870.1200	Acute Dermal Toxicity	Yes	Yes	Yes
870.1300	Acute Inhalation Toxicity	Yes	Yes	Yes
870.2400	Acute Eye Irritation	Yes	Yes	Yes
870.2500	Acute Dermal Irritation	Yes	Yes	Yes
870.2600	Skin Sensitization	Yes	Yes	Yes
870.3100	90-Day Oral Toxicity in Rodents	Yes	Yes	Yes
870.3150	90-Day Oral Toxicity in Non-Rodents	Yes	Yes	Yes
870.3200	21/28-Day Dermal Toxicity	Yes	Yes	Yes
870.3250	90-Day Dermal Toxicity	CR	No	NA
870.3465	90-Day Inhalation Toxicity	CR	No	Yes <sup>2</sup>
870.3700	Prenatal Developmental Toxicity Study (Rat)	Yes	Yes	Yes
	Prenatal Developmental Toxicity Study (Rabbit)	Yes	Yes	No
870.3800	Reproduction and Fertility Effects	Yes	Yes	Yes
870.4100	Chronic Toxicity (Rodent)	Yes	Yes	Yes
870.4200	Carcinogenicity (Rat)	Yes	Yes	NA
	Carcinogenicity (Mouse)	Yes	Yes	Yes
870.5100	Bacterial Reverse Mutation Test	Yes	Yes	Yes
870.5300	<i>in vitro</i> Mammalian Cell Gene Mutation Test	Yes <sup>1</sup>	Yes	Yes
870.5375	<i>in vitro</i> Mammalian Chromosome Aberration Test		Yes	
870.5385	Mammalian Bone Marrow Chromosomal Aberration Test	Yes <sup>1</sup>	No	Yes
870.5395	Mammalian Erythrocyte Micronucleus Test		Yes	
870.6100	Delayed Neurotoxicity of Organophosphorus Substances (Acute, Hen)	CR	No	NA
	Delayed Neurotoxicity of Organophosphorus Substances (28-Day, Hen)	CR	No	NA
870.6200	Neurotoxicity Screening Battery (Acute, Rat)	Yes	Yes	Yes
	Neurotoxicity Screening Battery (90-Day, Rat)	Yes	No	Yes <sup>2</sup>
870.6300	Developmental Neurotoxicity Study	CR	No	NA
870.7200	Companion Animal Safety	CR	No	NA
870.7485	Metabolism and Pharmacokinetics	Yes	Yes	Yes
870.7600	Dermal Penetration	CR	No	NA
870.7800	Immunotoxicity	Yes	Yes	Yes

CR: Conditionally Required

NA: Not Applicable

<sup>1</sup> Either guideline study type may be used to satisfy the data requirement (e.g., 870.5300 or 870.5375)

<sup>2</sup> Requirement waived by HASPOC on 10 April 2014 – TXR 0056942

## A.2 Toxicity Profiles

**Table A.2.1: Acute Toxicity Profile**

Guideline	Study Type	MRID	Results	Toxicity Category
870.1100	Acute Oral Toxicity	46684003	LD <sub>50</sub> = 134/138 mg/kg	II
870.1200	Acute Dermal Toxicity	47097627	LD <sub>50</sub> > 5000 mg/kg	IV
870.1300	Acute Inhalation Toxicity	47097628	LC <sub>50</sub> = 1.96 mg/L	III
870.2400	Acute Eye Irritation	47097629	Minimal irritation	III
870.2500	Acute Dermal Irritation	47097627	Not irritating	IV
870.2600	Dermal Sensitization	47097630	Positive (unacceptable study): in lieu of an acceptable dermal sensitization study demonstrating otherwise, TRB/RD recommends this chemical be labeled a dermal sensitizer.	---

**Table A.2.2: Subchronic, Chronic, and Other Toxicity Profiles**

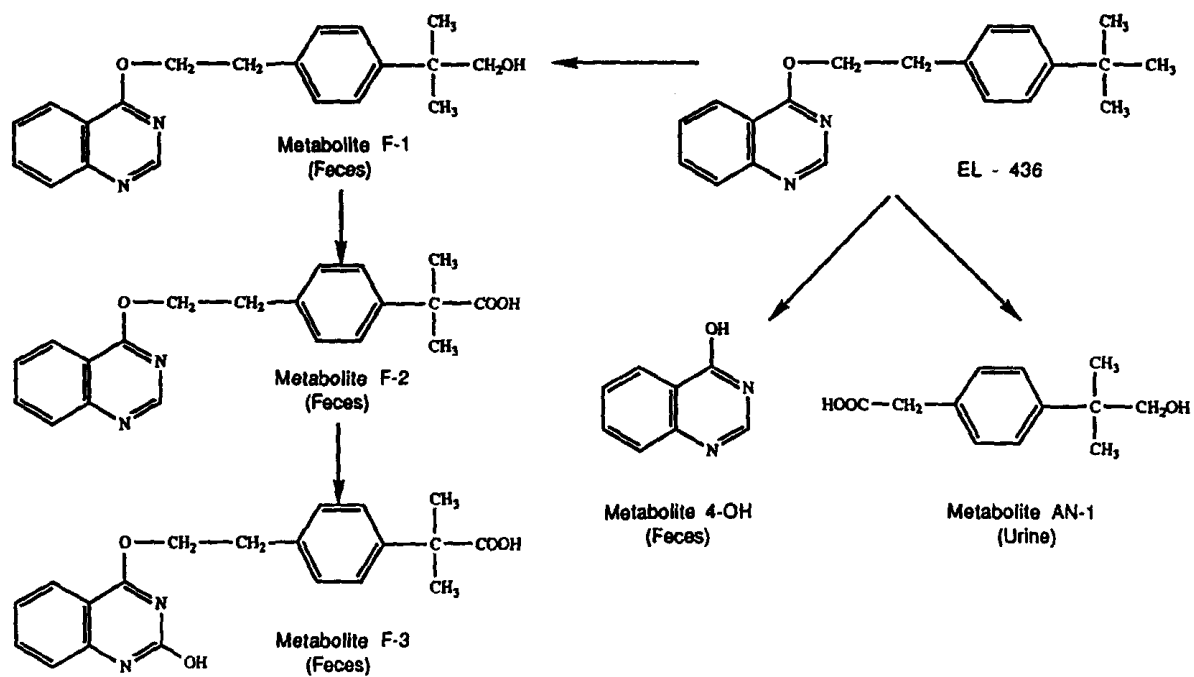
Guideline	Study Type	MRID (year) / Doses / Classification	Results
870.3100	90-Day Oral Toxicity in Rodents (Rat)	45029904 (1992) Dietary Concentration (ppm): 0, 15, 45, 150, 450 Dose (mg/kg/day): M: 0, 1.0, 3.0, 9.6, 28.7 F: 0, 1.2, 3.5, 11.5, 33.0 Acceptable / Guideline	NOAEL (mg/kg/day): M = 9.6 F = 11.5 LOAEL (mg/kg/day): M = 28.7 F = 33.0 Based on decreased body weight and food consumption.
		45029905 (1992) Gavage Dose (mg/kg/day): M: 0, 1, 3, 10, 30 F: 0, 1, 3, 10, 30 Acceptable / Guideline	NOAEL (mg/kg/day): M = 10 F = 10 LOAEL (mg/kg/day): M = 30 F = 30 Based on decreased body weight and food consumption/efficiency.
	90-Day Oral Toxicity in Rodents (Hamster)	45029903 (1992) Gavage Dose (mg/kg/day): M: 0, 5, 25, 75, 150 F: 0, 5, 25, 50, 100 Acceptable / Guideline	NOAEL (mg/kg/day): M = 25 F = 25 LOAEL (mg/kg/day): M = 75 F = 50 M: Based on decreased body weight, reduced testes and prostate weights, and testicular hypospermatogenesis F: Based on decreased body weight
870.3150	90-Day Oral Toxicity in Non-Rodents (Dog)	45029901 (1992) Dietary Concentration (ppm): Information was not available Dose (mg/kg/day): M: 0, 1, 5, 15 F: 0, 1, 5, 15 Acceptable / Guideline	NOAEL (mg/kg/day): M = 5 F = 5 LOAEL (mg/kg/day): M = 15 F = 15 Based on decreased body weight and food consumption/efficiency.
870.3200	21/28-Day Dermal Toxicity (Rabbit)	48143805 (1992) Dose (mg/kg/day): M: 0, 100, 315, 1000 F: 0, 100, 315, 1000 Acceptable / Non-Guideline	<u>Systemic</u> NOAEL (mg/kg/day): M = 1000 F = 1000 LOAEL (mg/kg/day): M > 1000 F > 1000
870.3465	90-Day Inhalation Toxicity	Study was not submitted	Study requirement waived by HASPOC TXR 0056942 (10 April 2014)
83-3 870.3700	Prenatal Developmental Toxicity Study (Rat)	45029911 (1989) Gavage Dose (mg/kg/day): F: 0, 3, 10, 40 Acceptable / Guideline	<u>Maternal</u> NOAEL (mg/kg/day) = 10 LOAEL (mg/kg/day) = 40 Based on findings (as early as GD 6-9) of decreased food intake and food efficiency.  <u>Developmental</u> NOAEL (mg/kg/day) = 40 LOAEL (mg/kg/day) > 40

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profiles			
Guideline	Study Type	MRID (year) / Doses / Classification	Results
	Prenatal Developmental Toxicity Study (Rabbit)	45029912 (1990) Gavage Dose (mg/kg/day): F: 0, 3, 13, 60 Acceptable / Non-Guideline  <i>The 60 mg/kg/day dose was excluded due to an unusually high number of mortalities that were not treatment related.</i>	<u>Maternal</u> NOAEL (mg/kg/day) = 13 LOAEL (mg/kg/day) > 13  <u>Developmental</u> NOAEL (mg/kg/day) = 13 LOAEL (mg/kg/day) > 13
83-4 870.3800	Reproduction and Fertility Effects (Rat)	46684001 (1991) Gavage Dose (mg/kg/day): M: 0, 1, 5, 25 F: 0, 1, 5, 25 Acceptable / Guideline	<u>Parental</u> NOAEL (mg/kg/day) = 5 LOAEL (mg/kg/day) = 25 Based on excessive salivation and decreased body weight and food intake.  <u>Reproductive</u> NOAEL (mg/kg/day) = 25 LOAEL (mg/kg/day) > 25  <u>Offspring</u> NOAEL (mg/kg/day) = 5 LOAEL (mg/kg/day) = 25 Based on decreased weight gain during lactation.
83-1 870.4100	Chronic Toxicity (Dog)	45029906 (1993) Dietary Concentration (ppm): Information was not available Dose (mg/kg/day): M: 0, 1, 5, 12 F: 0, 1, 5, 12 Acceptable / Guideline	NOAEL (mg/kg/day): M = 5 F = 5 LOAEL (mg/kg/day): M = 12 F = 12 Based on decreased body weight and food consumption, and food efficiency.
870.4200	Carcinogenicity (Hamster)	45029913 (1992) Gavage Dose (mg/kg/day): M: 0, 2, 15, 30 F: 0, 2, 15, 35 Acceptable / Guideline  <i>The Registrant's justification for using hamsters can be found in MRID 44742910</i>	NOAEL (mg/kg/day): M = 2 F = 15 LOAEL (mg/kg/day): M = 15 F = 35 M: Based on decreased body weight gain F: Based on decreased body weight No evidence of carcinogenicity
870.4300	Combined Chronic Toxicity/ Carcinogenicity (Rat)	45029907 (1992) Dietary Concentration (ppm): 0, 10, 100, 200, 400 (M) 450 (F) Dose (mg/kg/day): M: 0, 0.46, 4.5, 9.2, 18.3 F: 0, 0.57, 5.7, 11.5, 25.9 Acceptable / Guideline	NOAEL (mg/kg/day): M = 9.2 F = 11.5 LOAEL (mg/kg/day): M = 18.3 F = 25.9 Based on decreased body weight, food consumption, and food efficiency.  No evidence of carcinogenicity
870.5100	Bacterial Reverse Mutation Test (Salmonella typhimurium)	44742909 (1989) Applied Dose (µg/plate): ±S9: 0, 187.5, 375, 750, 1500, 3000 Acceptable / Guideline	±S9: Negative up to 3000 µg/mL in the absence of cytotoxicity with precipitation above this concentration.
870.5300	<i>in vitro</i> Mammalian Cell Gene Mutation Test (Mouse Lymphoma Cells)	44742908 (1989) Applied Dose (µg/mL): -S9: 0, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 20.0 +S9: 0, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0 Acceptable / Guideline	-S9: Negative, severely cytotoxic at concentrations up to 10 µg/mL +S9: Positive at concentrations (up to 12 µg/mL) that were severely cytotoxic (10-20% survival)

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profiles			
Guideline	Study Type	MRID (year) / Doses / Classification	Results
870.5375	<i>in vitro</i> Mammalian Chromosome Aberration Test (Chinese Hamster Ovary cells)	44742907 (1989) Applied Dose (µg/mL): -S9: 0, 0.1, 0.5, 1.0 +S9: 0, 40 50, 60 Acceptable / Guideline	± S9: Negative for clastogenic/aneugenic activity up to concentrations that reduced cell survival by ≈50% (1 µg/mL-S9; 60 µg/mL+S9). Compound precipitation was evident at levels ≥ 24 µg/mL +/- S9.
870.5395	Mammalian Erythrocyte Micronucleus Test (Mouse)	44742904 (1989) Gavage Dose (mg/kg): M: 0, 400, 800, 1600 F: 0, 400, 800, 1200 Acceptable / Guideline	Negative for clastogenic/aneugenic activity in mouse bone marrow up to the highest dose tested in males/females (1600/1200 mg/kg, repeated on two days).  In a preliminary study, the median lethal doses (MLD) were 3191/ 2430 mg/kg (M/F).
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture (Rat Hepatocytes)	44742906 (1989) Dose (µg/mL): -S9: 0, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 5.0 Acceptable / Guideline	Negative up to cytotoxic concentrations (≥0.5 to 1.0 µg/mL).
---	Unscheduled DNA Synthesis ( <i>in vitro</i> and <i>in vivo</i> )	45029908 (1989) Dose (µg/mL): -S9: 0, 180, 600 Acceptable / Non-Guideline	Negative for DNA damage and repair in this <i>in vivo/in vitro</i> test system up to the maximum tolerated dose (600 mg/kg).
870.5915	<i>in vivo</i> Sister Chromatid Exchange Assay (Mouse)	44742905 (1989) Gavage Dose (mg/kg): M: 0, 500, 1000, 2000 Unacceptable / Guideline  <i>Unacceptable due to inadequate number of test animals (each data point had 3 males which is lower than the guideline recommended 5/sex/dose)</i>	Negative in this cytogenetic assay (no increase in SCE) of bone marrow from male CD-1 mice treated with doses up to levels that produced death (2000 mg/kg).
870.6200	Neurotoxicity Screening Battery (Acute Rat)	48814001 (2012) Gavage Dose (mg/kg): M: 0, 20, 65, 130 F: 0, 20, 60, 120 Acceptable / Guideline	NOAEL (mg/kg/day): M = 20 F = 20 LOAEL (mg/kg/day): M = 65 F = 60 Based on mild dehydration in females.
	Neurotoxicity Screening Battery (Subchronic Rat)	Study has not been submitted	Study requirement waived by HASPOC TXR 0056942 (10 April 2014)
870.7485	Metabolism and Pharmacokinetics (Rat)	44742901 (1992) Gavage Dose (mg/kg): Single: 1, 30 Repeated: 1 Acceptable / Guideline	<u>Absorption</u> Absorption was determined to be 65.09% of the administered dose (AD). The urine contained 3.75% AD.  <u>Distribution</u> Fenazaquin residues were found in low levels throughout the rat with detectable levels in a broad range of organs (i.e. brain, kidneys, and liver) as well as in the residual carcass. The residue levels in the rat organs and tissues were <0.04% AD. The rat carcass without the previously mentioned organs contained ≤1.6% AD.

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profiles			
Guideline	Study Type	MRID (year) / Doses / Classification	Results
		48907401 (2012) – Tier 2 Study Gavage Dose (mg/kg): Single: 1 Acceptable / Guideline	<p><u>Metabolism</u></p> <p>Non-metabolized fenazaquin was higher in feces (1.0-15.0% AD) than in urine (&lt;0.5% AD) and some of the major metabolites were identified including AN-1 (urine) in addition to the fecal metabolites F-1, F-2 and F-3. The metabolic pathway of fenazaquin involved cleavage of the ether bond, resulting in the formation of the respective alcohol (4-OH quinazoline metabolite) and carboxyl acid (AN-1) derivatives. Other biotransformation reactions included oxidation of one of the methyl groups on the alkyl side chain to produce either an alcohol (F-1) or carboxylic acid (F-2) metabolites. Finally, hydroxylation at the O-ether alkyl moiety of F-1 or the 2-position of the quinazoline ring of F-2 resulted in F-1A and F-3 metabolites, respectively.</p> <p><u>Elimination</u></p> <p>The majority (89.5-107.7%) of elimination in the rat occurred within 168 hours. There was no radiolabel in the expired air and no evidence for bioaccumulation. Based on excretion and tissue residue data, bioavailability is conservatively estimated at about 20% of an administered dose.</p>
870.7600	<i>in vitro</i> Dermal Penetration (Human & Rat)	48012905 (2007) Study is not acceptable without an <i>in vivo</i> guideline OPPTS 870.7600 study submission	Preliminary review of the study indicates a dermal absorption of 0.48-7.33%.
870.7800	Immunotoxicity (Rat)	48459503 (2011) Gavage Dose (mg/kg/day): F: 0, 15, 30, 37.5/45 Acceptable / Non-Guideline	<p><u>Systemic Toxicity</u></p> <p>NOAEL (mg/kg/day) = 15 LOAEL (mg/kg/day) = 30 Based on clinical signs (general ataxia/hypo-activity) (also seen after a single dose).</p> <p><u>Immunotoxicity</u></p> <p>NOAEL (mg/kg/day) = 37.5 LOAEL (mg/kg/day) &gt; 37.5</p>
NA	Potential of XDE-436 Analogues to Induce Hepatic Hypertrophy and Peroxisome Acyl-CoA Oxidase Activity (Mouse)	44742903 (1993) Acceptable / Non-Guideline	Fenazaquin and several of its analogs (with varying susceptibilities to metabolism of the ether bond or the alkylbenzene substituents) were assessed for their ability to increase liver peroxisomal fatty acyl-CoA oxidase (FAO, a marker of peroxisomal proliferation) and relative liver weight in groups of five CD-1 female mice. The FAO peroxisomal activity data indicate that oxidation of the t-butyl substituent on the alkylbenzene moiety (to the corresponding carboxylic acid) of fenazaquin and related compounds appears to be the critical step for hepatocellular peroxisome proliferation.

## Appendix B. Proposed Metabolic Pathways for Fenazaquin (EL-436) in the Rat

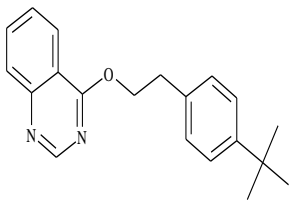


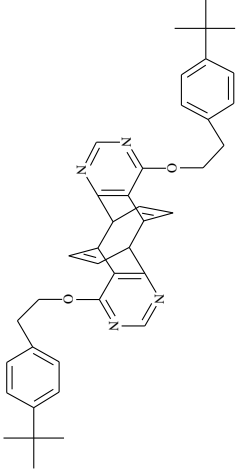
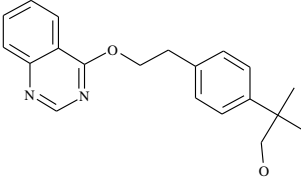
## Appendix C. Physical/Chemical Properties

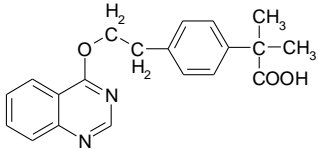
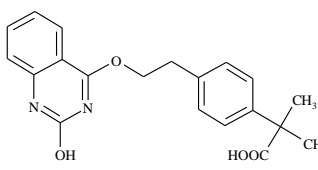
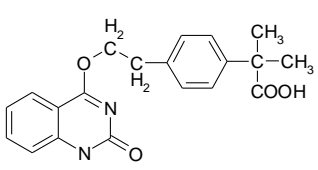
**Table C1. Physicochemical Properties of Fenazaquin.**

Parameter	Value	Reference
Melting point/range	77.5-80°C	Evaluation on Fenazaquin, Issue No. 150, Pesticides Safety Directorate, Depart. for Environment, Food, and Rural Affairs, U.K., March 1996
pH	Not determined due to low solubility	
Relative Density	1.16 at 21°C	
Water solubility (20°C)	0.102 mg/L at pH 5 & 7 0.135 mg/L at pH 9	
Solvent solubility (g/L at 23°C)	acetonitrile 33-50 acetone 400-500 n-chlorobutane >500 chloroform >500 dichloromethane >600 ethyl acetate 400-500 dimethylformamide 300-400 ethylene glycol <5 hexane 33-50 isopropanol 50-100 methanol 50-100 toluene >500 N-methyl-2-pyrrolidone >500	
Vapor pressure (25°C)	1.9 x 10 <sup>-5</sup> Pa; 1.4 x 10 <sup>-7</sup> mmHg 16 x 10 <sup>-5</sup> Pa 35 X 10 <sup>-5</sup> Pa	
Dissociation constant, pK <sub>a</sub>	2.44	
Octanol/water partition coefficient, Log(K <sub>ow</sub> )	5.71 at 25°C; 5.51 at 20°C	
UV/visible absorption spectrum	A <sub>max</sub> 215 nm ε = 41,588 L mol <sup>-1</sup> cm <sup>-1</sup>	

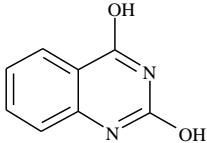
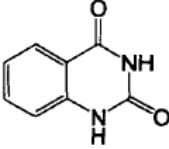
**Appendix D. Structure of Fenazaquin and its major metabolites/degradates**

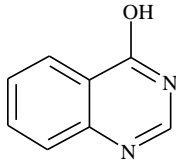
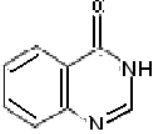
<b>Summary of Metabolites and Degradates</b>			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
Fenazaquin  	Apple (30% mature) (7 DAT)	66.4 (0.363) P	
		76.0 (0.461) Q	
	Apple (30% mature) (28 DAT)	48.0 (0.070) P	
		39.7 (0.085) Q	
	Orange (63 DAT)	65.5 (0.295) P	
		55.4 (0.500) Q	
	Grapes (28 DAT)	63.0 (0.939) P	
		46.4 (1.22) Q	
	Grapes (49 DAT)	39.1 (0.14) P	
		26.7 (0.662) Q	
	Corn grain (20 DAT)	23.1 (0.003) Q	
		Not analyzed P	
	Corn stover (20 DAT)	48.4 (2.95) Q	
		29.8 (1.98) P	
	Radish root (rotational)	30 (0.031) Q 30 day PBI	15 (0.007) Q 120 day PBI
		27 (0.026) P	16 (0.009) P
	Lettuce immature (rotational 30 day PBI)		8.0 (0.004) Q
			7.3 (0.004) P
	Wheat straw (rotational 30 day PBI)		1.7 (0.002) Q
			0.8 (0.002) P
	Muscle (Goat)		N/D P Not analyzed Q
	Fat (Goat)	83.0 (0.073) Q	
		77.3 (0.085) Q	
	Kidney (Goat)		N/D P and Q
	Liver (Goat)		N/D P and Q
	Milk (Goat)	15.4 (0.004) Q	
		47.1 (0.016) P	
	Muscle, thigh (Chicken)	68.8 (0.011) P	5.0 (0.003) Q
	Fat, subcutaneous (Chicken)	83.2 (0.134) Q	
		88.8 (0.159) P	
	Fat, omental (Chicken)	94.9 (0.147) Q	
		89.2 (0.156) P	
	Liver (Chicken)		4.6 (0.004) Q
			N/D P
	Eggs (Chicken)	13.0 (0.003) P	2.1 (0.003) Q
	Rat		1 – 21% of residue in feces
	Water	Major residue	

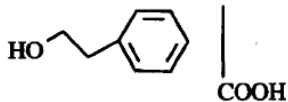
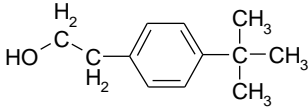
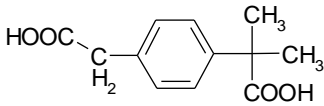
Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
<b>Fenazaquin Dimer</b> 	Apple (30% mature) (7 DAT)	24.6 (0.135) P 10.1 (0.061) Q	
	Apple (30% mature) (28 DAT)	27.4 (0.040) P 19.4 (0.041) Q	
	Grapes (28 DAT)		N/D P and Q
	Corn grain (20 DAT)		7.7 (0.001) Q Not analyzed P
	Corn stover (20 DAT)	19.8 (1.20) Q 54.3 (3.61) P	
	Goat		Tissues – not found
	Chicken		Tissues – not found
	Rat		Not found
	Water		Not found
<b>2-Methyl-2-{4-[2-(quinazolin-4-yloxy)-ethyl]-phenyl}-propan-1-ol</b> (Metabolite F1) (Metabolite C) 	Apple (30% mature) (7 DAT)		1.0 (0.005) P [or metabolite L] N/D Q
	Apple (30% mature) (28 DAT)		3.3 (0.005) P [or metabolite L] 0.4 (0.001) Q
	Grapes (28 DAT)		9.1 (0.136) P 4.3 (0.112) Q
	Grapes (49 DAT)	12.9 (0.046) P	
			3.3 (0.062) Q
	Goat		Tissues – not found
	Chicken		Tissues – not found
	Rat		5 – 9.4% residue in feces
	Water		Not found
	Rat	16 – 23% of TRR in feces	

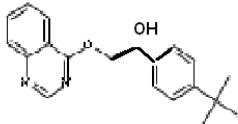
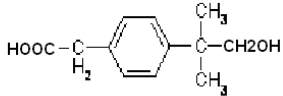
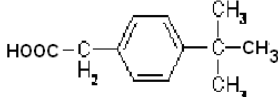
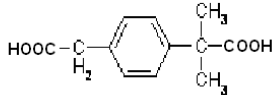
Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
2-Methyl-2-(4-(2-((4-quinazolinyloxy)ethyl)phenyl)-propionic acid. (Metabolite 5) (Metabolite F2) 	Water		Identified as present
(Metabolite D) (M29) (Metabolite F3) (Metabolite 2 in the drinking water memo)  2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid  2-Methyl-2-(4-{2-[(2-oxo-1,2-dihydroquinazolin-4-yl)oxy]ethyl}phenyl)propanoic acid   	Apple (105 day PHI)		0.8 (<0.001) Q
	Corn stover (20 DAT)		0.5 (0.033) Q
			N/D P
	Radish root (30 day PBI)		3.8(0.004) Q
			3.2 (0.003) P
	Muscle (Goat)	20.0 (0.005) P	
		Not analyzed Q	
	Fat (Goat)		0.9 (0.001) P
			N/D Q
	Kidney (Goat)	28.6 (0.010) Q	
		25.3 (0.023) P	
	Liver (Goat)	13.7 (0.054) Q	
		14.9 (0.106) P	
	Milk (Goat)		1.8 (0.001) Q
			2.9 (0.001) P
Eggs (Chicken)	Liver (Chicken)		7.0 (0.003) P
			N/D Q
	Eggs (Chicken)	13.0 (0.003) P	1.4 (0.002) Q
4(2-(4(1,1dimethylethyl)-phenyl)ethoxy)quinazalone	Orange (191 day PHI)		8.1 (0.029) P
			4.9 (0.016) Q
	Corn stover (20 DAT)		1.2 (0.073) Q
			0.5 (0.030) P

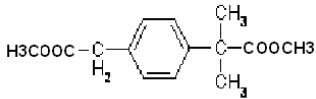
Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
4-[2-(4-tert-butyl-phenyl)-ethoxy]-quinazolin-2-ol  2-Oxy-fenazaquin 2-Hydroxy-fenazaquin (Metabolite F) (Metabolite 1)	Radish root (rotational, 30 day PBI)		3.8 (0.004) Q
			4.2 (0.004) P
	Radish top (rotational, 30 day PBI)		3.3 (0.001) Q
	Wheat straw (rotational, 30 day PBI)		0.9 (0.001) Q
			0.4 (0.001) P
	Fat (goat)		1.1 (0.001) Q
			0.9 (0.001)
	Liver (goat)		Previously reported at 4 – 10% TRR in a marginal study.
	Rat		Not found, but implied by oxidative metabolism and presence of F3 ('fenazaquin acid') in feces.
	Water		8.1% of applied chemical
2-(4-(1,1-dimethyl-phenyl)ethyl)-2-(formylaminobenzoate)  1-(4-Tert-butylphenyl)-2-(quinazolin-4-yloxy)ethanone (Metabolite H) (Metabolite 4)	Grapes	(76 DAT)	2.7 (0.028)P
			N/D Q
	Water		Present but not quantified
	Goat		Not found
	Chicken		Not found
	Rat		Not found
	Apple (30% mature) (7 DAT)		N/D P
			1.9 (0.012) Q
			N/D P

Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
Dihydroxyquinazoline (Metabolite I)  And its tautomer Quinazolidione or Benzoyleneurea 	Apple (30% mature) (28 DAT)		4.4 (0.009) Q
	Orange		N/D
	Grapes (28 DAT)		3.8 (0.099) Q
	Grapes (49 DAT)		4.1 (0.101) Q
	Grapes (76 DAT)	26.2 (0.248) Q, including 14% from base hydrolysis.	
	Muscle, thigh (Chicken)	63.3 (0.038) Q	
	Fat, subcutaneous (Chicken)	14.9 (0.024) Q	
	Fat, omental (Chicken)		3.2 (0.005) Q
	Liver (Chicken)	52.9 (0.046) Q	
	Eggs (Chicken)	82.4 (0.117) Q	
	Goat		Not found
	Rat		Not found
	Water		Identified – amount not reported

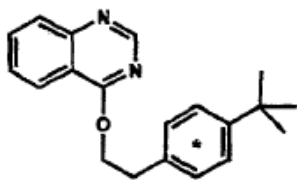
Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
4-Hydroxyquinazoline 4-Quinazolinol (Metabolite J)  And its tautomer Quinazolidinone 	Apple (30% mature) (7 DAT)		0.4 (0.003) Q
	Apple (30% mature) (28 DAT)		3.2 (0.007) Q
	Orange		N/D
	Grapes (49 DAT)		1.6 (0.040) Q
	Corn stover (20 DAT)		6.9 (0.419) Q
	Radish root (30 day PBI)		8.7 (0.009) Q
	Radish top (30 day PBI)		3.3 (0.001) Q
	Lettuce immature (rotational 30 day PBI)		4.0 (0.002) Q
	Wheat straw (rotational 30 day PBI)		4.3 (0.005) Q
	Wheat hay (rotational 30 day PBI)		8.0 (0.010) Q
	Wheat forage (rotational 30 day PBI)		8.1 (0.003) Q
	Kidney (goat)		5.7 (0.002) Q
	Liver (goat)		1.9 (0.007) Q
	Milk (goat)		23.1 (0.006) Q
	Rat		Minor component of feces reported in the proposed metabolic scheme

Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
	Water	Minor to major depending upon conditions	
2-(4-(2-hydroxyethyl)phenyl)-2-methyl propanoic acid (Metabolite K) 	Grapes (76 DAT)		4.1 (0.043) P
Tertiarybutylphenyl ethanol or 4-(1,1-Dimethylethyl)benzene-ethanol or 4-tert-butylphenethyl alcohol (Metabolite L) 	Apple (0 DAT)		0.6 (0.005) P
	Grapes (28 DAT)		3.0 (0.08) P
	Corn stover (20 DAT)		1.8 (0.119) P
	Radish root (30 day PBI)		1.0 (0.001) P
	Rat		Not found, but implied present by general oxidative metabolism and presence of metabolite AN-1
	Water	Minor to major depending upon conditions	
2-(4-carboxymethylphenyl)-2-methylpropanoic acid (Metabolite G) (Metabolite M34) 	Kidney (goat)		8.8 (0.008) P
	Liver (goat)	15.3 (0.109) P	
	Rat		Not found (in feces)
	Water		Minor identified product

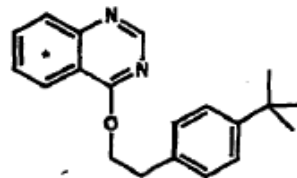
Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
Metabolite F1A 	Rat		0.8-2.6% of TRR in rat feces
Metabolite AN-1 	Rat	24 – 29% TRR in rat urine	
(4-tertbutylphenyl)acetic acid (Metabolite 6) 	Water		Minor identified product
	Rat		Not found in feces, but implied by general oxidative metabolism and presence of metabolite AN-1
1-[3-(carboxymethyl)phenyl]-2-methylpropionic acid 	Water		Minor identified product

Summary of Metabolites and Degradates			
Chemical Name (other names in parentheses) and Structure	Matrix	Percent TRR (PPM) <sup>1</sup>	
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)
Methyl-2-[4-(2-oxoethyl)phenyl]-2-methylpropanoate  	Water		Minor identified product
<p><i>Apple</i>; 45029914 &amp; 45029917; 31 or 125 mg ai/L; unknown X rate; post-emergence (spray painted to fruit), early season or late season; 0, 7, 14, 28 and 105-day PHI (early season) or 0 and 70-day PHI (late season).</p> <p><i>Orange</i>; 45054401 &amp; 44742913; 0.4 lb ai/A; 1X rate; post-emergence (foliar), early season or late season; 0, 28, 112 and 191-day PHI (early season) or 0, 19, and 63-day PHI (late season).</p> <p><i>Grape</i>: 48350005 (1) Early season, 0.013 lb ai/acre, foliar, berry diameter 3 – 6 mm. Samples 0, 49, 76 DAT. (2) Late season, 0.013 lb ai/acre, foliar; berry diameter 10 – 15 mm. Samples 0, 28 DAT.</p> <p><i>Corn</i>: 48350008. 0.45 lb ai/acre (1X) at milk stage. Samples: corn grain and stover at 20 DAT.</p> <p><i>Confined Rotational</i>: 48073883. 0.45 lb ai/acre (1X) to ground. Lettuce, wheat, garden beet sowed at PBIs of 30, 120, and 365 days.</p> <p><i>Goat</i>: 48350007. 0.79 mg/kg/bw/day [P] and 0.84 mg/kg bw/day [Q] or about 12 ppm based on feed; 5 consecutive days.</p> <p><i>Hen</i>: 48350008. 0.97 mg/kg bw/day [Q] and 0.98 mg/kg bw/day [P] or about 12 ppm based on feed; 7 consecutive days.</p>			

<sup>1</sup> Fenazaquin radiolabeled in the phenyl ring [P] or on the quinazoline ring [Q]. The label positions are depicted below.



\* denotes position of radiolabel, uniformly labeled in the phenyl ring



\* denotes position of radiolabel, uniformly labeled in the phenyl ring of the quinazoline